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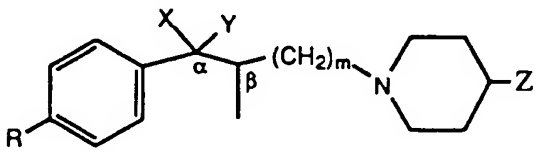
(54) Phenylalkanolamine derivatives as antagonists of the NMDA receptor.

(57) Compounds of the formula



I

wherein
R is hydrogen, hydroxy, or aryl lower alkyloxy;
X is hydrogen;
Y is hydroxy or hydrogen;
or both X and Y taken together are oxygen;
Z is aryl lower alkyl; and
m is an integer from 1 to 4
or a diastereomer or an enantiomer thereof, except, the R,R diastereomer of formula I, wherein X is hydrogen, Y is hydroxy, R is benzyloxy, Z is benzyl, and m is 1, or pharmaceutically acceptable salts thereof, reduce adverse effects of toxic injury to central neurons and thus are useful in the treatment of ischemia, stroke, hypoxia and are NMDA receptor antagonists.

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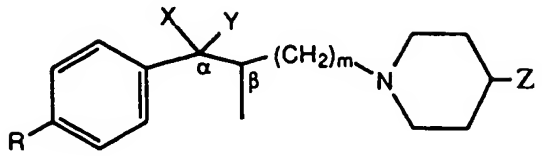
The invention relates to compounds of the formula



I

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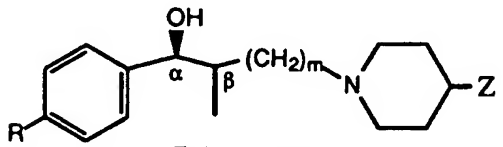
R is hydrogen, hydroxy, or aryl lower alkyloxy;
X is hydrogen;
Y is hydroxy or hydrogen;
or both X and Y taken together are oxygen;
Z is aryl lower alkyl; and
m is an integer from 1 to 4

or enantiomers or diastereomers thereof, except, the R,R diastereomer of formula I, wherein X is hydrogen, Y is hydroxy, R is benzyloxy, Z is benzyl, and m is 1,

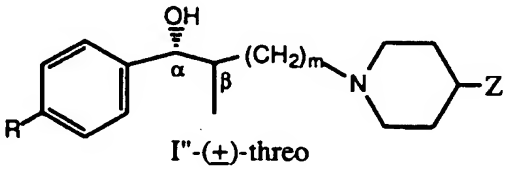
or pharmaceutically acceptable salts thereof.

The compounds of formula I may contain two asymmetric centers at the α- and β-positions. Accordingly, the compounds of formula I can be diastereomers, that is, erythro (R^*,S^*) or threo (R^*,R^*) isomers.

As used herein, the terms "erythro" and "threo" refer to the relative configurations of the hydroxy, when present, and the methyl substituent, at the α- and β-positions of the compounds of formula I' and I" as shown below, which are racemates. However, the emantiomers of the erythro and threo racemates of formula I' and II" are part of the invention.



I'-(±)-erythro



I"-(±)-threo

The compounds of formula I, reduce adverse effects of neurotoxic injury and thus are useful in the treatment of neurodegenerative diseases, such as, stroke, ischemia, hypoxia, hypoglycemia, epilepsy, and the like.

Objects of the present invention are the compounds of formula I and their pharmaceutically acceptable salts per se and for use as therapeutically active substances, the manufacture of these compounds, medicaments containing these and the manufacture of such medicaments, as well as the use of compounds of formula I and their pharmaceutically acceptable salts in the control or prevention of illnesses or in the improvement of health, especially in the control or prevention of neurodegenerative diseases, such as stroke, ischemia, hypoxia, hypoglycemia, epilepsy, and the like. Objects of the invention are also intermediate compounds of formulas VII, VIII, XII, XIII, XIV and XV.

In another aspect, the present invention relates to a method of reducing adverse effects of toxic injury to central neurons which comprises administering to a host in need of such treatment an effective amount of a compound of formula I.

The following definitions of the general terms used in the present description apply irrespective of wether the terms in question appear alone or in combination.

As used herein, the term "alkyl", either alone or in combination, denotes a straight or branched-chain alkyl group containing from 1 to 7 carbon atoms, preferably 1 to 4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl and the like. The term "aryl", either alone or in combination, denotes a group derived from an aromatic hydrocarbon, such as, for example, phenyl or naphthyl, preferably phenyl, which may be unsubstituted or substituted by one or more substituents selected from alkyl, alkoxy, hydroxy or halogen, preferably hydroxy or halogen.

The term "halogen" denotes chlorine, iodine, fluorine or bromine. The term "alkoxy" denotes an alkyl group, as defined earlier which is attached via oxygen atoms, examples of alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert.butoxy, and the like.

In preferred compounds of formula I, R is hydrogen or hydroxy, Y is hydroxy, Z is unsubstituted benzyl or phenylethyl and m is 1 or 2.

In a particularly preferred embodiment of a compound of formula I, R is hydroxy, Y is hydroxy, Z is unsubstituted benzyl and m is 1.

Exemplary compounds of formula I are:

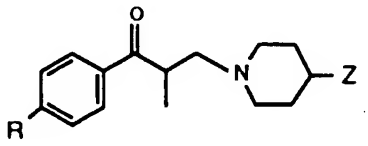
(R*,S*)-rac.-β-Methyl-α-[4-(phenylmethoxy)phenyl]-4-(phenylmethyl)-1-piperidinepropanol;
(R*,S*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol;
rac.-4-[2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]propyl]phenol;
(R*,S*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinebutanol;
rac.-4-[2-methyl-4-[4-(phenylmethyl)-1-piperidinyl]butyl]phenol;
(S)-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone;
[R-(R*,S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol;
[S-(R*,S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol;
rac.-(2-methyl-3-phenylpropyl)-4-(phenylmethyl)piperidine; and
(R*,R*)]-rac-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol.

Particularly preferred compounds of formula I are:

(R*,S*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol;
[R-(R*,S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol; and
[S-(R*,S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol.

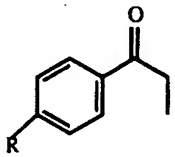
In accordance with the present invention the compounds of formula I and their pharmaceutically acceptable salts can be prepared by a process which comprises

a) for the manufacture of compounds of the formula



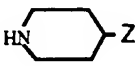
IA

wherein R and Z are as above,
reacting a compound of the formula



II

wherein R is as above,
with a compound of the formula



III

wherein Z is as above,
and with paraformaldehyde, or

b) for the manufacture of compounds of the formula I, wherein X and Y are hydrogen, catalytically hydrogenating a compound of the formula I, wherein X and Y taken together and are oxygen, in the presence of a suitable catalyst such as palladium on carbon, or

c) for the manufacture of compounds of the formula I, wherein X is hydrogen and Y is hydroxy, reducing a compound of the formula I, wherein X and Y taken together and are oxygen, with hydrogen in the presence of a suitable catalyst such as palladium on carbon, or with a complex alkali metal hydride, such as lithium aluminium or potassium borohydride, or

d) for the manufacture of compounds of the formula I, wherein X and Y are hydrogen, reducing a compound of the formula I, wherein X is hydrogen and Y is hydroxy with borane methylsulfide complex,

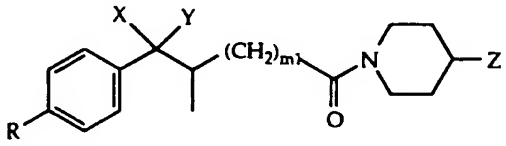
or

e) for the manufacture of compounds of the formula I, wherein R is OH, debenzylating a compound of the formula I, wherein R is benzyloxy, or

f) for the manufacture of compounds of the formula I, wherein R is aryl lower alkoxy, reacting a compound of formula I, wherein R is hydroxy, with a corresponding aryl alkylhalide, or

g) for the manufacture of compounds of the formula I, wherein X and Y are taken together and are oxygen, oxidizing a compound of the formula I, wherein X and Y are hydrogen or X is hydrogen and Y is hydroxy, or

h) for the manufacture of compounds of the formula I, wherein X and Y are hydrogen or X is hydrogen and Y is hydroxy, reducing a compound of the formula

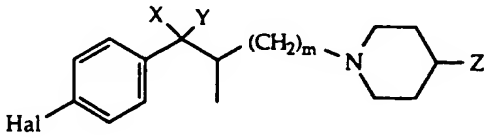


XVIII

wherein R, X, Y and Z are as above and ml is 1-3,

with a complex alkali metal hydride or borane methylsulfide, or

i) for the manufacture of compounds of the formula I, wherein R is hydrogen, dehalogenating a compound of the formula



IXX

wherein X, Y and Z are as above, and m is 1-4,

with hydrogen in the presence of a suitable catalyst such as palladium on carbon, or

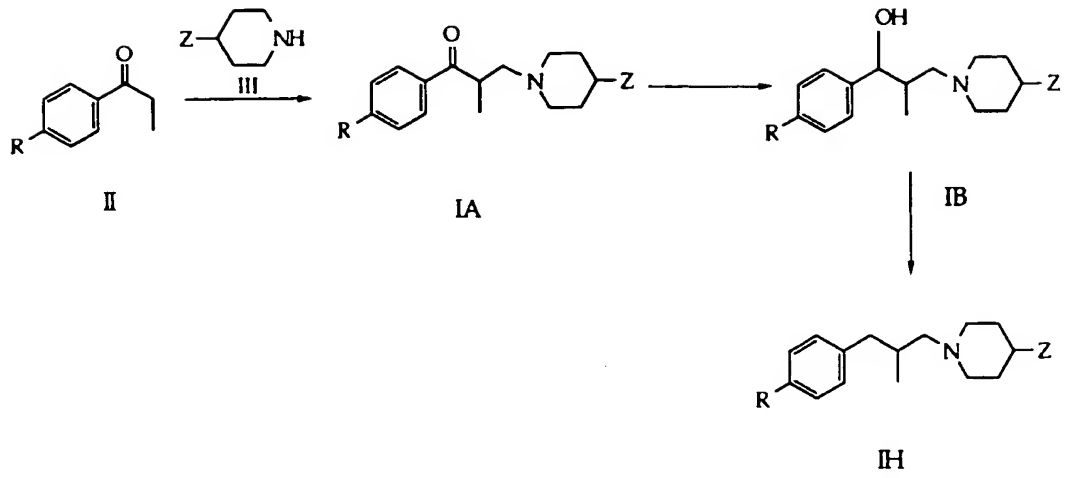
j) for the manufacture of optically pure compounds of the formula I, resolving a racemic mixture into its enantiomeric components, or

k) for the manufacture of racemic compounds of the formula I, wherein X and Y are taken together and are oxygen, racemizing a corresponding optically pure compound, and

l) if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

The reaction conditions for the above process variants a)-l) are described in more details hereinafter in Reaction Schemes 1-7

SCHEME 1



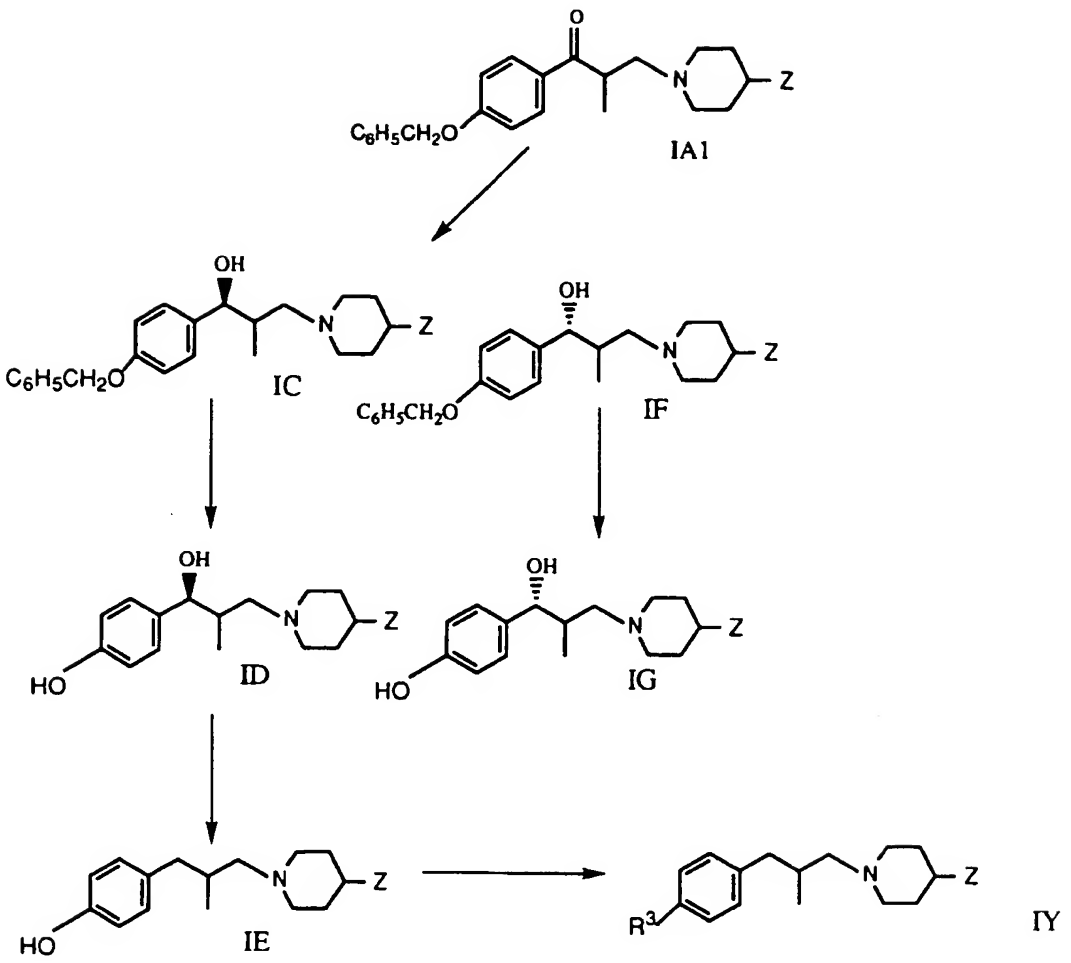
wherein R and Z are as described above.

As set forth in Scheme 1, a compound of formula II, a known compound, is reacted with a compound of formula III, a known compound, or which can be prepared by known methods, and paraformaldehyde to form a corresponding compound of formula IA. In carrying out this reaction, temperature and pressure are not critical. Generally, it is preferred to utilize temperatures from room temperature to 100°. The reaction is usually carried out in water, ethanol or dimethylformamide, preferably dimethylformamide.

A compound of formla IA is reduced by catalytic hydrogenation in the presence of palladium on carbon at room temperature in, preferably, ethanol and at 50 p.s.i. The racemic erythro isomer of formula IB can be isolated from the mixture by chromatography.

A compound of formula IB can be reduced to a corresponding compound of formula IH by borane-methylsulfide complex in tetrahydrofuran.

Scheme 2

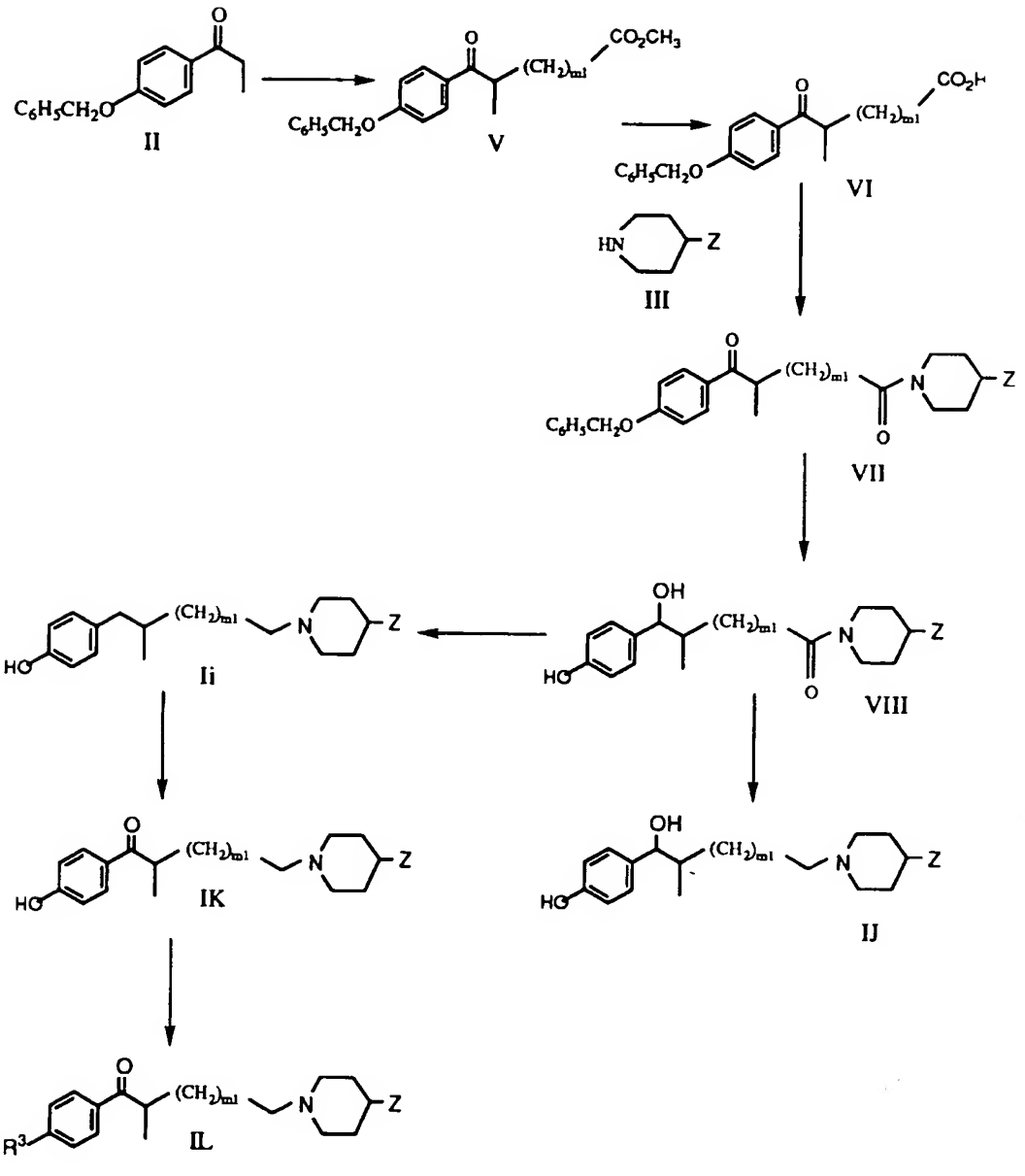


wherein Z is as described above and R^3 is aryl lower alkyloxy.

A compound of formula IA1 forms a mixture of racemic isomers, compounds of formulas IC and IF when reduced in the presence of a complex alkali metal hydride, such as, lithium aluminum hydride in tetrahydrofuran. Such a mixture can be separated by chromatography. The compounds of formulas IC and IF are debenzylated separately to the racemic erythro (R*,S*) and threo (R*,R*) diastereomers, compounds of formulas ID and IG, respectively. The reaction is carried out by catalytic transfer hydrogenation using 10% palladium on carbon and ammonium formate in acetone at reflux temperature. The compound of formula ID is converted to the racemic compound of formula IE by treating with borane-methylsulfide complex in tetrahydrofuran at reflux temperature.

A compound of formula IE can be converted to a corresponding compound of formula IY by reacting with an aryl alkylhalide in acetone in the presence of potassium carbonate.

SCHEME 3



wherein m1 is 1-3, R^3 is aryl lower alkyloxy and Z is as described above.

As set forth in Scheme 3, the compound of formula II, a known compound, is converted to a compound of formula V by treating with an alkyl haloester, such as, methyl bromoacetate, methyl 3-bromopropionate, methyl 4-bromobutyrate and the like in an organic solvent such as ether or tetrahydrofuran, preferably tetrahydrofuran in the presence of a condensing agent, such as, hexamethyldisilazide. Generally, it is preferred to carry out this reaction at from about -50 • to about -78 • .

A compound of formula V is hydrolyzed by an alkali metal hydroxide, such as, sodium or potassium hydroxide, in tetrahydrofuran, to form the corresponding compound of formula VI, preferably at room temperature.

A compound of formula VI is condensed with a compound of formula III, a known compound or which can be prepared by known methods, in the presence of a coupling agent, such as, 1,3-dicyclohexylcarbodiimideand 1-hydroxybenzotriazole to form a corresponding compound of formula VII. Generally, this

reaction is carried out in dimethylformamide at room temperature.

A compound of formula VII is reduced to the corresponding compound of formula VIII, by hydrogenation in the presence of palladium on carbon in acetic acid at room temperature and preferably at 50 p.s.i.

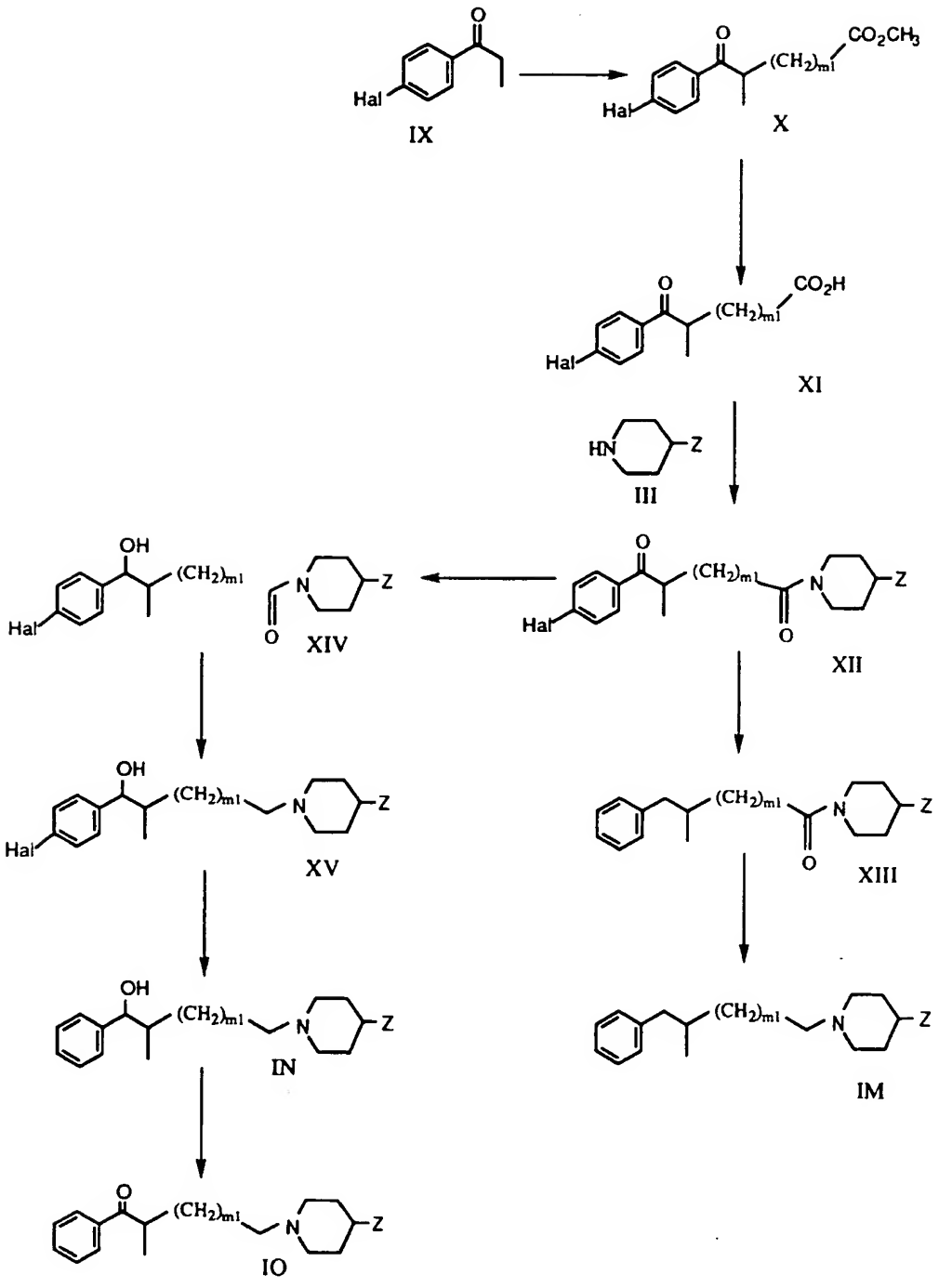
A compound of formula VIII is reduced to a corresponding compound of formula IJ with a complex alkali metal hydride, such as, lithium aluminum hydride or a di(lower-alkyl)aluminum hydride, such as, diisobutyl aluminum hydride. Preferably, the reaction is carried out in a tetrahydrofuran or ether solvent.

Alternatively, a compound of formula VIII is reduced to a corresponding compound of formula Ii by treating with boranemethylsulfide complex in tetrahydrofuran, preferably at room temperature.

A compound of formula Ii can be oxidized to a corresponding compound of formula IK with chromic acid in a solvent, such as, for example, acetic acid, water-acetic acid or pyridine.

A compound of formula IK can be converted to a corresponding compound of formula IL by reacting with an aryl alkylhalide in acetone in the presence of potassium carbonate.

SCHEME 4



wherein Hal is halogen, ml is 1-3 and Z is as described in the specification.

As set forth in Scheme 4, a compound of formula IX, a known compound or which can be prepared by known methods, can be converted to a corresponding compound of formula X by treating with an alkyl haloester, such as, methyl bromoacetate, methyl 3-bromoproprionate, methyl 4-bromobutyrate and the like in an organic solvent, such as, ether or tetrahydrofuran, preferably, tetrahydrofuran in the presence of a condensing agent, such as, hexamethyldisilazide.

A compound of formula X can be hydrolyzed to a corresponding compound of formula XI by treating with alkali metal hydroxide, such as, sodium or potassium hydroxide in tetrahydrofuran, preferably at room temperature.

A compound of formula XI can be condensed with a compound of formula III, a known compound or which can be prepared by known methods, in the presence of a coupling agent, such as, 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole to form a corresponding compound of formula XII. Generally, this reaction is carried out in dimethylformamide at room temperature.

A compound of formula XII can be reduced to a corresponding compound of formula XIII by hydrogenation in the presence of palladium on carbon in ethanol at room temperature and preferably at 50 p.s.i.

A compound of formula XIII can be reduced to a corresponding compound of formula IM by treating with a complex alkali metal hydride, such as, lithium aluminum hydride in tetrahydrofuran, preferably, at room temperature.

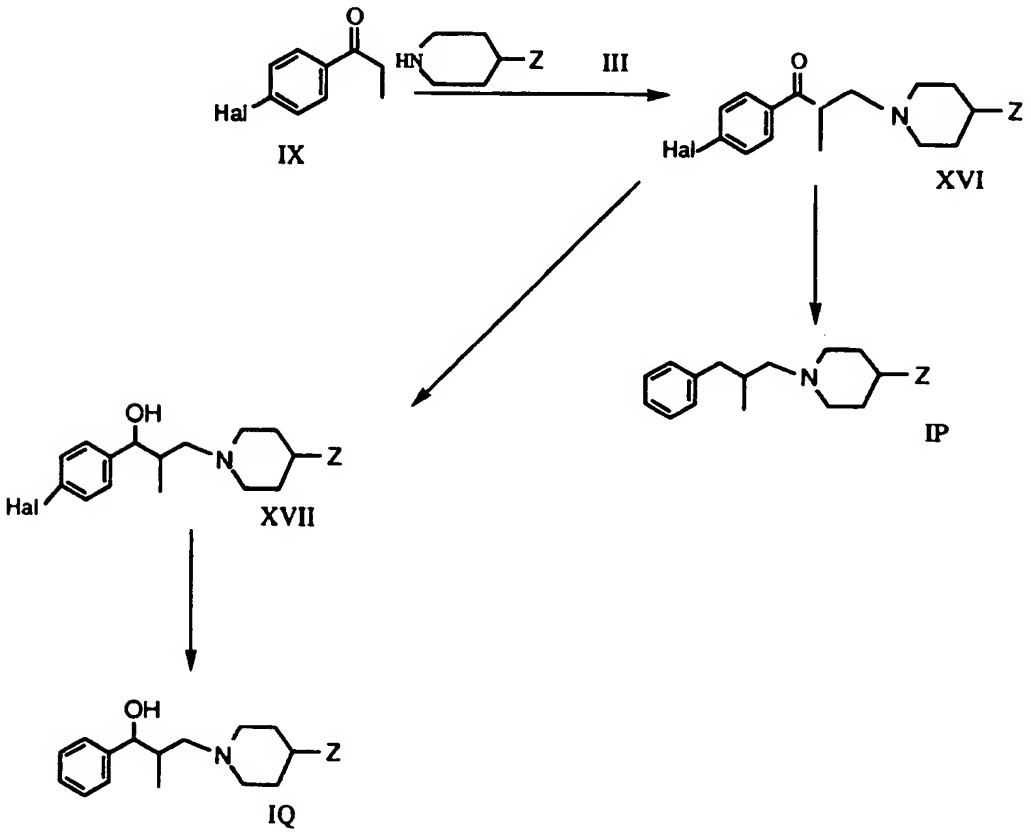
Alternatively, a compound of formula XII can be reduced to a corresponding compound of formula XIV by potassium borohydride reduction in, preferably, a mixture of ethanol-acetic acid at room temperature.

A compound of formula XIV can be reduced to a corresponding compound of formula XV with a complex alkali metal hydride, such as, lithium aluminum hydride or a di(loweralkyl)aluminum hydride, such as, diisobutyl aluminum hydride. Preferably, this reaction is carried out in a tetrahydrofuran or ether solvent.

A compound of formula XV can be converted to a corresponding compound of formula IN by catalytic hydrogenation in the presence of palladium on carbon at room temperature and at 50 p.s.i.

A compound of formula IN can be oxidized to a corresponding compound of formula IO with chromic acid in a solvent such as acetic acid, water-acetic acid or pyridine.

SCHEME 5



wherein Hal is halogen, and Z is as described above.

As set forth in Scheme 5, a compound of formula IX, a known compound or which can be prepared by known methods, is reacted with a compound of formula III, a known compound or which can be prepared by known methods, and paraformaldehyde to form a corresponding compound of formula XVI. Generally, the reaction is carried out in the temperature range of from room temperature to 100° and, preferably, in dimethylformamide solvent.

A compound of formula XVI is reduced to a corresponding compound of formula IP by catalytic hydrogenation in the presence of palladium on carbon in a protonic solvent, such as, methanol, ethanol, preferably, ethanol, at room temperature under pressure of 50 p.s.i.

Altenatively, a compond of formula XVI is reduced to a corresponding compound of formula XVII by potassium borohydride reduction.

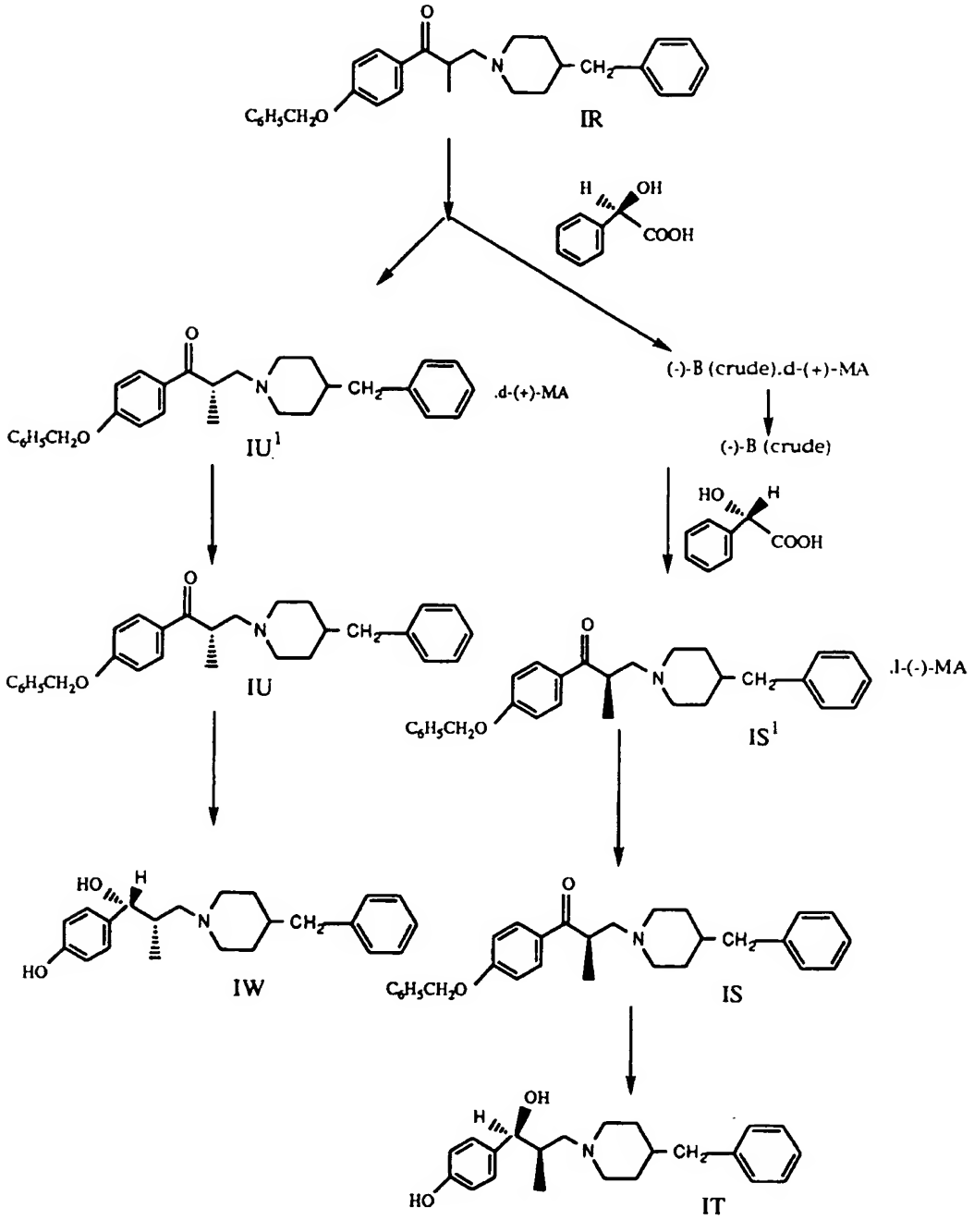
A compound of formula XVII can be converted to a corresponding compound of formula IQ by catalytic hydrogenation in the presence of palladium on carbon at room temperature and at 50 p.s.i. in ethanol.

The enantiomers and diastereomers of the compounds of formula I form another aspect of the invention. The resolution of a particular compound of formula IR, that is, rac-2-[methyl-1-[4-(phenylmethoxy) phenyl]-3-[4-(phenylmethyl)-1-piperidinyl)-1-propanol is shown in Scheme 6. The resolution of other compounds of formula I may require, for example, other conventional resolving agents.

The erthyro and threo racemates of formula I can be similarly resolved by using other conventional resolving agents.

If desired, either enantiomer can be racemized, for example, as set forth in Scheme 7, for renewed resolution.

SCHEME 6



As set forth in Scheme 6, the compound of formula IR, prepared as provided in Scheme I, in acetone is treated with a resolving agent such as d-(+)-mandelic acid, which is also called (S)-α-hydroxybenzoic acid, and the resulting solution is allowed to crystallize at about room temperature. The crystals are a salt of formula IU¹ comprising the resolving agent and the (+)-enantiomer of the compound of formula IR. The soluble salt is that of the (-)-enantiomer of the compound of formula IR in solution with the resolving agent.

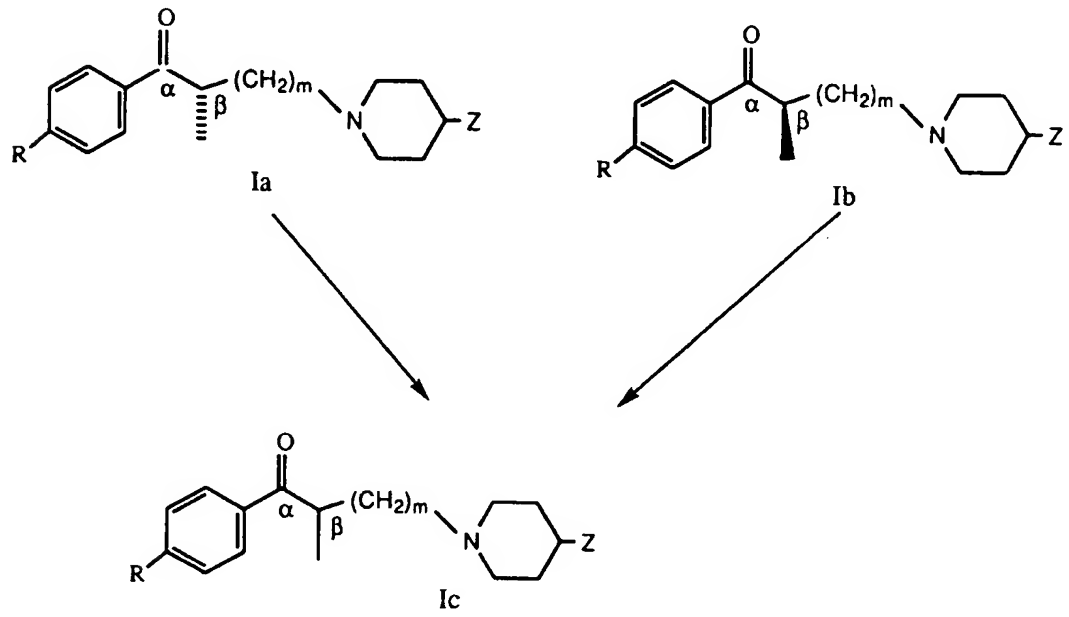
The above solution is concentrated and the residue (-)-B(crude) d-(+)-MA, wherein MA is mandelic acid and B is a base, is treated in water with a base, such as, sodium hydroxide or more preferably with

concentrated ammonium hydroxide and the resulting suspension is extracted with an organic solvent, such as, methylene chloride and concentrated to give the crude (-)-enantiomer. The crude (-)-enantiomer can be further purified by dissolving in hot acetone and treating the resulting solution with 1 -(-)-mandelic acid, also known as (R)-α-hydroxybenzoic acid. The crystals are a salt of formula IS' of the resolving agent and the (-)enantiomer of the compound of formula IR. The salt can be suspended in water and treated with a base, such as, concentrated ammonium hydroxide, and the resulting suspension can be extracted with an organic solvent, such as, methylene chloride. The (-)-enantiomer of formula IS can be isolated from the solution by evaporation of the solvent and can be used for reduction to the compound of formula IT.

The salt of formula IU' can be treated in water with a base, such as, sodium hydroxide or more preferably with concentrated ammonium hydroxide, then the aqueous suspension is extracted with an organic solvent, such as, methylene chloride and concentrated to obtain the (+)-enantiomer of formula IU, which can be used for reduction to the compound of formula IW.

Compounds of formulas IU and IS are reduced to (-)-erythro and (+)-erythro compounds of formulas IW and IT, respectively, by hydrogenation in the presence of palladium on carbon in acetic acid at room temperature and 50 p.s.i.

SCHEME 7



wherein R and Z are as described above.

As set forth in Scheme 7, racemization of either enantiomer of formula Ia or Ib can be carried out with an alkali metal hydroxide, such as, sodium hydroxide in an alcoholic solvent, such as, methanol, ethanol and the like, at reflux temperature.

The compounds of formula I are active as non-competitive NMDA receptor antagonists and are therefore, useful as neuroprotecting agents, for example, in the treatment of injury to central neurons associated with ischemia, hypoxia, hypoglycemia, epilepsy, Huntington's disease or Alzheimer's disease.

The activity of compounds of formula I can be demonstrated by the following:

1. ^{3}H-MK 801 (dizocilpine) binding in vitro

Method

^{3}H-MK 801 binding was performed as described in Ransom, R.W. and Stec, N.L., J. Neurochem. 51 (1988) 830-836, with extensively washed rat brain membranes prepared according to the following scheme. Frozen whole rat brain was thawed and cerebellum and medulla oblongata were removed on ice. The tissue

was then homogenized with an Ultra Turrax (maximal energy) during 30 sec at 4 °C in 50 volumes of Tris•HCl (5mM) with ethylenediaminetetraacetic acid (EDTA) disodium (10 mM, pH = 7.4). The homogenate was centrifuged at 48'000 x g for 10 min. The pellet was rehomogenized with the same volume of the same buffer and the homogenate was then incubated at 37 °C for 10 min. After centrifugation the pellet was rehomogenized under the same conditions and frozen at -80 °C in 35 ml fractions for at least 16 hours and not more than 2 weeks.

On the day of experiment, the homogenate was thawed 15 minutes at 37 °C and centrifuged as above. The pellet was rehomogenized in 25 volumes of Tris•HCl buffer (5mM, pH = 7.4) and the homogenate was recentrifuged. This procedure was repeated twice. The final pellet was rehomogenized in 25 volumes of Tris•HCl buffer (5 mM, pH = 7.4) related to the original wet weight and used as such in the assay. Final concentration in the assay was 20 mg/ml.

300 µl of tracer solution (final concentration 5 nM ^{3}H-MK 801) in Tris•HCl buffer (5 mM, pH 7.4) were incubated with 100 µl of test solution (100 µl of Tris•HCl buffer for the total binding or 100 µl of buffer plus N-(1-(2-thienyl)cyclohexyl)piperidine (TCP) (final concentration 0.1 µM) for non specific binding). Glutamate, glycine and spermidine (final concentrations 1nM) were added together in 100 µl volume. 500 µl of homogenate (final concentration 20 mg/ml) were then added in the plastic reaction tubes. After 2 hours of incubation at room temperature, the suspension was filtered (Whatmann GF/B, presoaked in 0.05% polyethylenimine for 2 hours) and washed 5 times with 3 ml of cold buffer. The air-dried (3 min) filters were counted in 10 ml of Ultima-gold (Packard) after agitation (10 min.) and standing for 2 hours at 3 °C in vials.

The results are set forth in Table I.

TABLE I

Compound	IC_{50} µM
Ex. 5	0.3
Ex. 6	0.53
Ex. 7	1.3
Ex. 8	0.005
Ex. 9	0.006
Ex. 10	0.15
Ex. 12	0.9
Ex. 15	0.0013
Ex. 16	0.003
Ex. 21	1.4

These are high affinity values determined from biphasic displacement curves.

2. Acute Glutamate Neurotoxicity

Method

Single cell suspensions were prepared from embryonic rat cortices (E16-17) by digestion with dispase 2.4 U/ml (BOEHRINGER) and subsequent trituration with fire polished pasteur pipettes. The cells were then plated on poly-D-lysine (SIGMA) coated 96 well microtiter plates (NUNC, 10^5 cells/well) in a total volume of 100 µl Dulbeccos modified essential medium (DMEM, GIBCO) supplemented with 10% horse serum and penicillin/streptomycin (SIGMA). 5 days later, non-neuronal cell division was halted by exposure to 10^{-5} cytosine arabinoside combined with a 50% exchange of culture medium. The cultures were used for neurotoxicity assays from 8-12 days in vitro.

Acute glutamate toxicity was performed according to D.W. Choi. J. Koh and S. Peters, J. Neurosci. 8 (1988) 185-196, in 100 µl of a control salt solution (CSS: 120 mM NaCl, 5.4 mM KCl, 0.8 mm $MgCl_2$, 1.8 mM $CaCl_2$, 25 mM Tris HCl (pH 7.4 at 25 °C) and 15 mM glycose) with 500 µM glutamate for 5 to 30 minutes at room temperature with or without addition of substances to be tested.

After washing, the cultures were maintained in 100 µl CSS overnight at 37 °C. For quantitation of neurodegeneration, lactate dehydrogenase was measured in the cell culture supernatant as described by J.G. Klingman, D.M. Hartley and D.W. Choi, J. Neurosci. Meth. 31 (1990) 47-51 using a BIOMEK workstation (BECKMAN). Percentage of neuronal degeneration was calculated taking the difference of unprotected and maximally protected cultures (with a reference NMDA-receptor antagonist) as 100%. From

dose response curves IC_{50} values were calculated.

The results are set forth in Table II.

TABLE II

Compound	IC_{50} μM
Ex. 5	1.9
Ex. 6	3.5
Ex. 7	64
Ex. 8	0.04
Ex. 9	0.11
Ex. 10	0.12
Ex. 12	66
Ex. 15	0.06
Ex. 16	0.08
Ex. 21	13

The compounds of formula I above form pharmaceutically acceptable acid addition salts. Thus, the compounds of the present invention form pharmaceutically acceptable acid addition salts including, but not limited to HCl, HBr, HNO_3, H_2SO_4, H_3PO_4, CH_3SO_3H, $CH_3C_6H_4SO_3H$, CH_3CO_2H, C_6H_5COOH, gulonic, tartaric, mandelic and succinic.

The compounds of formula I and their salts, as herein described, can be incorporated into standard pharmaceutical dosage forms, for example, they are useful for oral or parenteral application with the usual pharmaceutical adjuvant material, for example, organic or inorganic inert carrier materials, such as, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkyleneglycols and the like. The pharmaceutical preparations can be employed in a solid form, for example, as tablets, suppositories, capsules, or in liquid form, for example, as solutions, suspensions or emulsions. Pharmaceutical adjuvant materials can be added and include preservatives, stabilizers, wetting or emulsifying agents, salts to change the osmotic pressure or to act as buffers. The pharmaceutical preparations can also contain other therapeutically active substances.

The daily dose of compounds of formula I to be administered varies with the particular compound employed, the chosen route of administration and the recipient. Representative of a method for administering the compounds of formula I is by the oral and parenteral type administration route. An oral formulation of a compound of formula I is preferably administered to an adult at a dose in the range of from 150 mg to 1.5 gm per day. A parenteral formulation of a compound of formula I is preferably administered to an adult at a dose in the range of from 5 to 500 mg per day.

The invention is further illustrated in the following examples.

EXAMPLE 1

rac.-3- Methyl-4-oxo-4-[4-(phenylmethoxy)phenyl]butanoic Acid Methyl Ester

To a solution of 5.5 ml (0.055 mol) of potassium hexamethyldisilazide (20 wt % in THF) in 20 ml of tetrahydrofuran chilled to -78°C was added dropwise a solution of 12.0 g (0.05 mol) of 4-benzyloxypropiophenone in 30 ml of tetrahydrofuran over a period of 20 minutes. After stirring at -78°C for 1 hr, a solution of 9.0 g (0.06 mol) of methyl bromoacetate in 25 ml of tetrahydrofuran (dry) was added dropwise to the reaction mixture over a period of 30 minutes at -78°C then stirred at this temperature for 1 hr and allowed to warm to room temperature. It was then poured onto 1N hydrochloric acid and extracted with ethyl acetate. The combined organic solutions were washed with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give 19.2 g of crude racemic-3-methyl-4-oxo-4-[4-(phenylmethoxy)-phenyl] butanoic acid methyl ester, which was chromatographed on silica gel (300 g). Elution of the column with methylene chloride-ethyl acetate (8:2; v/v), fractions 12-35 after removal of the solvent afforded 7.1 g (42%) of racemic-3-methyl-4-oxo-4-[4-(phenylmethoxy)phenyl] butanoic acid methyl ester b.p. 205-207°C (0.2 mmHg).

EXAMPLE 2

rac.-3-Methyl-4-oxo-4-[4-(phenylmethoxy)phenyl]butanoic Acid

A mixture of 11.2 g (0.0046 mol) of racemic-3-methyl-4-oxo-4-[4-(phenylmethoxy)phenyl]butanoic acid methyl ester, 120 ml of tetra-hydrofuran, 12 ml of water and 60 ml of 2N sodium hydroxide was stirred at room temperature for 3 hrs. The reaction mixture was diluted with water (30 ml) and extracted with methylene chloride. The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give 11.1 g of crude racemic-3-methyl-4-oxo-4-[4-(phenylmethoxy)phenyl]butanoic acid, which was crystallized from ethyl acetate to provide 9.6 g (69%) of racemic-3-methyl-4-oxo-4-[4-(phenylmethoxy)-phenyl]butanoic acid, m.p. 147-148 • C.

EXAMPLE 3

rac.-2-Methyl-1-[4-(phenylmethoxy)phenyl]-4-[4-(phenylmethyl)-1-piperidinyl]-1,4-butanedione

A mixture of 8.0 g (0.0027 mol) of racemic-3-methyl-4-oxo-4-[4-(phenylmethoxy)phenyl]butanoic acid, 4.8 g (0.027 mol) of N-benzyl-piperidine, 6.4 g (0.031 mol) of 1,3-dicyclohexylcarbodiimide and 4.0 g (0.029 mol) of 1-hydroxybenzotriazole in 200 ml of dry dimethyl-formamide was stirred at room temperature for 48 hrs. The reaction mixture was poured onto 1N hydrochloric acid and the aqueous suspension was extracted with ethyl acetate. The organic extracts were washed with 2N sodium hydroxide, then brine and dried ($MgSO_4$). Removal of the solvent gave a 14.7 g residue which was chroma-tographed on silica gel (220 g). Elution of the column with methylene chloride-ethyl acetate (90:10; v/v), fractions 7-15 after removal of the solvent afforded 9.8 g (80%) of racemic-2-methyl-1-[4- (phenyl-methoxy)phenyl]-4-[4-(phenylmethyl)-1-piperidinyl]-1,4-butanedione. Analytical sample was crystallized from ether, m.p. 99-100 • C.

EXAMPLE 4

(R*,S*)-rac.-4-Hydroxy-4-(4-hydroxyphenyl)-3-methyl-1-[4-(phenylmethyl)-1-piperidinyl]-1-butanone

A solution of 4.0 g (0.0087 mol) of racemic-2-methyl-1-[4-(phenylmethoxy)phenyl]-4-[4-(phenylmethyl)-1-piperidinyl]-1,4-butanedione in 125 ml acetic acid was hydrogenated with 1.5 g of palladium on carbon (10%) for 5.5 hrs at 50 psi at room temperature. The catalyst was filtered and the filtrate was concentrated at reduced pressure. The residue was partitioned between methylene chloride and dilute ammonium hydroxide. The organic extracts were washed with brine and dried ($MgSO_4$). Removal of the solvent gave a 3.1 g residue which was chromatographed on silica gel (110 g). The column was eluted with methylene chloride-ethyl acetate (2:8; v/v), fractions 23-34 after removal of the solvent gave 2.3 g of crude product which was crystallized from ethyl acetate-hexane to give 2.1 g (72%) of (R*,S*)-rac.-4-hydroxy-4-(4-hydroxyphenyl)-3-methyl-1-[4-(phenylmethyl)-1-piperidinyl]-1-butanone, m.p. 128-130 • C.

EXAMPLE 5

(R*,S*)-rac.-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinebutanol

To a mixture of 0.7 g (0.018 mol) of lithium aluminum hydride in 10 ml of tetrahydrofuran was added dropwise a solution of 1.0 g (0.0027 mol) of (R*,S*)-rac.-4-hydroxy-4-(4-hydroxyphenyl)-3-methyl-1-[4-(phenylmethyl)-1-piperidinyl]-1-butanone in 25 ml of dry tetrahydrofuran over a period of 10 minutes. The mixture was stirred at reflux for 2 hrs then cooled to room temperature and decomposed by a dropwise addition of ethyl acetate followed by hydrochloric acid. The reaction mixture was partitioned between ethyl acetate and dilute ammonium hydroxide. The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give 0.9 g of (R*,S*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinebutanol, which was crystallized from ethyl acetate to yield 0.6 g (63%) of pure base, m.p. 174-175 • C.

0.6 g (0.0017 mol) of the above base was treated with fumaric acid to give 0.7 g (86%) of (R*,S*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl) -1-piperidinebutanol • (E)-2-butenedioate as the hemihydrate, m.p. 90-92 • C.

EXAMPLE 6

rac.-4-[2-Methyl-4-[4-(phenylmethyl)-1-piperidinyl]butyl]phenol.

To a solution of 1.0 g (0.0027 mol) of (R*,S*)-rac.-4-hydroxy-4-(4-hydroxyphenyl)-3-methyl-1-[4-(phenylmethyl)-1-piperidinyl]-1-butanone in 30 ml of dry tetrahydrofuran was added dropwise over 10 minutes 3.3 ml (0.043 mol) of borane-methyl sulfide complex. The reaction mixture was stirred at room temperature for 0.5 hr then at reflux for 11 hrs. It was cooled to room temperature and decomposed by a dropwise addition of 20 ml of methanol followed by 2 ml of concentrated hydrochloric acid, which was then heated at reflux for 2 hrs. After removal of the solvent, the residue was partitioned between methylene chloride and dilute ammonium hydroxide. The combined methylene chloride extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed to give 1.1 g of a residue, which was chromatographed on silica gel (35 g). Elution of the column with ethyl acetate-methylene chloride (8:2, v/v) fractions 9-22, after removal of the solvent gave the crude product, which was crystallized from ether to provide 0.75 g (83%) of rac.-4-[2-methyl-4-[4-(phenylmethyl)-1-piperidinyl]butyl]phenol, m.p. 142-143 °C.

0.4 g (0.001 mol) of the above base in acetone on treatment with maleic acid afforded 0.3 g (67%) of rac.-4-[2-methyl-4-[4-(phenyl-methyl)-1-piperidinyl]butyl]phenol • maleate, m.p. 142-143 °C.

EXAMPLE 7

(R*,S*)-rac.-β-Methyl-α-[4-(phenylmethoxy)phenyl]-4-(phenylmethyl)-1-piperidinepropanol

To a suspension of 0.5 g (0.013 mol) of lithium aluminum hydride in 15 ml of anhydrous tetrahydrofuran was added dropwise a solution of 1.0 g (0.0023 mol) of rac.-2-[methyl-1-[4-(phenylmethoxy)phenyl-3- [4-(phenylmethyl)-1-piperidinyl]-1-propanone in 20 ml of anhydrous tetrahydrofuran over a period of 10 minutes. The reaction mixture was stirred at room temperature for 1 hr, then it was decomposed by dropwise addition of 10 ml of ethyl acetate followed by 30 ml of brine. The mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give 0.9 g a mixture of the racemic erythro and threo diastereomers in a ratio of 6:7. Chroma-tographic separation of the diastereomers was carried out on silica gel (60 g). Elution of the column with the chloroform-methanol-water-acetic acid [90:15:10:6; v/v], fractions 6 and 7 after removal of the solvent and crystallization from etherhexane gave 0.34 g (35%) of (R*,S*)-rac.-β-methyl-α-[4-(phenylmethoxy)phenyl]-4-(phenylmethyl)-1-piperidine-propanol, m.p. 83-84 °C.

A sample of the above base, on treatment with hydrogen chloride (anhydrous) in ethanol yielded (R*,S*)-rac.-β-methyl-α-[4-(phenyl-methoxy)phenyl]-4-(phenylmethyl)-1-piperidine propanol • HCl, m.p. 189-190 °C.

EXAMPLE 8

(R*,S*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol

A mixture of 0.8 g (0.0019 mol) of (R*,S*)-rac.-β-methyl-α-[4-(phenylmethoxy)phenyl]-4-(phenylmethyl)-1-piperidinepropanol, 0.8 g of ammonium formate and 0.8 g of palladium on carbon (10%) in 50 ml of acetone was stirred and refluxed for 1 hr. The catalyst was separated by filtration and the filtrate was concentrated under reduced pressure. The residue was partitioned between methylene chloride and dilute ammonium hydroxide. The methylene chloride extracts were washed with brine, dried ($MgSO_4$) then the solvent was removed under reduced pressure and the residue (0.6 g) in acetone was treated with hydrogen chloride (anhydrous). The resulting crystals were collected by filtration, dried to give 0.4 g (56%) of (R*,S*)-rac.-α-(-4-hydroxy- phenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol • HCl, m.p. 190-191 °C.

EXAMPLE 9

(R*,R*)-rac.-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol.

A mixture of 0.8 g (0.019 mol) of (R*,R*)-rac.-β-methyl-α-[4-(phenylmethoxy)phenyl]-4-(phenylmethyl)-1-piperidinepropanol, 0.8 g (0.012 mol) of ammonium formate and 0.8 g of palladium on carbon (10%) in 50 ml of acetone was stirred and refluxed for 1 hr. The catalyst was separated by filtration and the filtrate was concentrated *in vacuo*. The residue was partitioned between methylene chloride and dilute ammonium hydroxide. The organic extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed under

reduced pressure. The crude product 0.4 g was chromatographed on silica gel (28 g). Elution of the column with chloroform-methanol-water-acetone [90:15:10:6 (v/v)], fractions 15-30, after removal of the solvent and crystallization of the residue from ether-hexane yielded 0.15 g (24%) of (R*,R*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenyl-methyl)-1-piperidinepropanol, m.p. 132-133 °C.

0.5 g (0.0015 mol) of the above base and 0.17 g (0.0015 mol) of fumaric acid in ethanol afforded of (R*,R*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol•fumarate, m.p. 118-119 °C.

EXAMPLE 10

rac.-4-[2-Methyl-3-[4-(phenylmethyl)-1-piperidinyl]butyl]phenol.

To a solution of 2.0 g (0.059 mol) of (R*,S*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol, in 60 ml of anhydrous tetrahydrofuran was added dropwise 6.6 ml (0.086 mol) of borane-methyl sulfide complex. The reaction mixture was stirred at room temperature for 0.5 hr then heated at reflux for 17 hrs and decomposed by dropwise addition 20 ml of methanol followed by 8.0 ml of concentrated hydrochloric acid. After refluxing the mixture for 2 hrs, it was concentrated *in vacuo* and the residue was partitioned between methylene chloride and dilute ammonium hydroxide. The organic extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give 2.0 g of crude product which was crystallized from ether to provide 1.7 g (89%) of rac.-4-[2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]propy]phenol, m.p. 119-120 °C.

A sample of the above base, in acetone on treatment with hydrogen bromide (65%) gave rac.-4-[2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]propyl]phenol•HBr as the hemihydrate, m.p. 118-120 °C.

EXAMPLE 11

Resolution of rac.-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone

A mixture of 46.0 g (0.11 mol) of rac.-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone and 16.3 g (0.11 mol) of d-(+)-mandelic acid in 280 ml acetone was heated on the steam bath until clear solution obtained, then seeded with a few crystals of (+)-base d-(+)-mandelate and allowed to crystallize at room temperature for 18 hrs. The crystals were separated by filtration, washed with cold acetone and dried to yield 25.1 g (81%) of (S)-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone (1:1) molar (S)-α-hydroxybenzeneacetate, m.p. 135-137 °C, $[\alpha]_D^{25}$ + 42.1 ° (C 1.00 methanol).

EXAMPLE 12

(S)-2-Methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone

(S)-2-Methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone (S)-α-hydroxybenzeneacetate, 25.1 g (0.043 mol) was suspended in water (80 ml) and decomposed with dilute ammonium hydroxide. The resulting suspension was extracted with methylene chloride (3x200 ml). The combined methylene chloride solutions were washed with water, dried ($MgSO_4$) and removal of the solvent gave 17.4 g (94%) of (S)-2-methyl-1-[4-(phenylmethoxy) phenyl]-3-[4-(phenylmethyl-1-piperidinyl]-1-propanone, b.p. 225-230 °C (0.05 mmHg), $[\alpha]_D^{25}$ + 10.9 ° (C 1.00 methanol).

0.7 g (0.0016 mol) of the above base in ethyl acetate was treated with hydrogen chloride (anhydrous) to give 0.72 g (95%) of (S)-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl-1-piperidinyl]-1-propanone•HCl, m.p. 198-200 °C, $[\alpha]_D^{25}$ + 22.9 ° (C 1.00 methanol).

EXAMPLE 13

(R)-2-Methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone (1:1) molar (R)-α-Hydroxybenzeneacetate

The mother liquors obtained after removal of (S)-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone•(S)-α-hydroxybenzeneacetate were taken to dryness and in water (200 ml) was decomposed with dilute ammonium hydroxide. The resulting suspension was extracted with

methylene chloride (2x400 ml). The combined methylene chloride solutions were washed with water, dried ($MgSO_4$) and removal of the solvent gave 26.8 g of crude (R)-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-phenylmethyl)-1-piperi-dinyl]-1-propanone. 26.8 g (0.062 mol) of the crude base and 9.49 g (0.062 mol) of l-(-)-mandelic acid in 160 ml of acetone was heated on the steam bath until a clear solution was obtained, then seeded with a few crystals of (R)-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone (1:1) molar (R)-α-hydroxy-benzeneacetate and allowed to crystallize at room temperature for 18 hrs. The crystals were separated by filtration, washed with cold acetone and dried to yield 26.3 g (84%) of (R)-2-methyl-1-[4-(phenyl-methoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone (1:1) molar (R)-α-hydroxybenzeneacetate salt, m.p. 136-138 °C. The analytical sample was recrystallized from acetone, m.p. 136-138 °C, $[\alpha]_D^{25}$ -41.2 °(C 1.00 methanol).

EXAMPLE 14

(R)-2-Methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone

(R)-2-Methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone (1:1) molar (R)-α-hydroxybenzeneacetate, 26.3 g (0.045 mol) was suspended in water (100 ml) and decomposed with dilute ammonium hydroxide. The resulting suspension was extracted with methylene chloride (3x200 ml). The combined methylene chloride solutions were washed with water (100 ml), dried ($MgSO_4$) and removal of the solvent gave 18.7 g (96%) of (R)-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone, b.p. 227-231 °C (0.05 mmHg), $[\alpha]_D^{25}$ -9.1 ° (C 1.00 methanol).

0.7 g (0.0016 mol) of the above base in ethyl acetate was treated with hydrogen chloride (anhydrous) to give 0.71 g (93%) of (R)-2-Methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)]-1-propanone monohydrochloride, m.p. 197-199 °C. The analytical sample was recrystallized from ethanol, m.p. 197-199 °C, $[\alpha]_D^{25}$ -22.7 ° (C 1.00 methanol).

EXAMPLE 15

[R-(R*S*)]-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol

A solution of 5.0 g (0.013 mol) of (S)-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone in 100 ml of acetic acid was hydrogenated over 1.5 g of palladium on carbon (10%) at room temperature and 50 psi for 17 hrs. The catalyst was removed by filtration, the filtrate was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and dilute ammonium hydroxide. The ethyl acetate extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed to give 3.3 g of diastereomeric alcohols in a ratio of 9:1. To 3.3 g (0.0097 mol) of the crude base in acetone, was added 1.2 g (0.0098 mol) of benzoic acid. The resulting crystals were collected to give 3.7 g (62%) of [R-(R*S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol benzoate, m.p. 171-172 °C, $[\alpha]_D^{25}$ + 15.5 ° (C 1.00 methanol).

1.0 g (0.0021 mol) of the above salt was partitioned between ethyl acetate and dilute ammonium hydroxide. The ethyl acetate solutions were washed with brine and dried ($MgSO_4$). Removal of the solvent gave a residue, which was crystallized from ether-hexane to yield 0.7 g (91%) of [R-(R*S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol, m.p. 107-108 °C, $[\alpha]_D^{25}$ + 32.5 ° (C 1.00 methanol).

To 0.17 g (0.0005 mol) of the above base in acetone was added 0.08 g (0.0005 mol) of p-chlorobenzic acid. The resulting crystals were collected to provide 0.16 g (65%) of [R-(R*S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol 4-chlorobenzoate. The analytical sample was recrystallized from acetonitride, m.p. 140-142 °C, $[\alpha]_D^{25}$ + 14.5 ° (C 1.00 methanol).

EXAMPLE 16

[S-(R*S*)]-α-(4-Hydroxyphenyl)-β-methyl]-4-(phenylmethyl)-1-piperidinepropanol

A solution of 5.0 g (0.013 mol) of (R)-2-methyl-1-[4-(phenylmethoxy)phenyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone in 100 ml of acetic acid was hydrogenated over 1.5 g of palladium on carbon (10%) at room temperature and 50 psi for 17 hrs. The catalyst was removed by filtration, the filtrate was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and dilute ammonium hydroxide. The ethyl acetate extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed

under reduced pressure to give 3.0 g of diastereomeric alcohols in a ratio of 9:1. To 3.0 g (0.0088 mol) of crude base in acetone was added 1.0 g (0.0088 mol) of benzoic acid. The resulting crystals were collected to give 3.6 g (60%) of pure [S-(R*S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol benzoate, m.p. 171-172 °C, $[\alpha]_D^{25}$ - 15.2° (C 1.00 methanol).

1.0 g (0.0021 mol) of the above base was partitioned between ethyl acetate and dilute ammonium hydroxide. The ethyl acetate solution was washed with brine and dried ($MgSO_4$). Removal of the solvent and after recrystallization from ether-hexane gave 0.7 g (91%) of [S-(R*S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol, m.p. 107-108 °C, $[\alpha]_D^{25}$ - 32.5° (C, 1.00, methanol).

EXAMPLE 17

Racemization of (R)-2-Methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone

To 0.5 g of sodium hydroxide in 8.0 ml of methanol was added 0.5 g (0.001 mol) of (R)-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone [$[\alpha]_D^{25}$ - 10.5° (C, 1.00, methanol)]. The reaction mixture was heated at reflux for 17 hrs then cooled to room temperature and diluted with brine. The aqueous suspension was extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give 0.4 g (80%) of crude rac.-2-[methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone [$[\alpha]_D^{25}$ - 0.25° (C, 1.00, methanol)].

0.4 g (0.001 mol) of the above base on treatment with hydrogen chloride (anhydrous) in ethyl acetate afforded 0.35 g (65%) of rac.-2-[methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone monohydrochloride m.p. 192-193 °C. .

EXAMPLE 18

rac-1-(4-Benzyloxyphenyl)-2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone

A mixture of 9.6 g (0.04 mol) of 4-benzyloxypropiophenone, 1.2 g of paraformaldehyde, 1.75 g (0.01 mol) of 4-benzylpiperidine hydro-chloride and 1 ml of concentrated hydrochloric acid in 40 ml dimethylformamide was stirred and heated at 55-60 °C for 17 hours. The reaction mixture was poured onto about 200 ml 1N hydrochloric acid, then precipitate was filtered, and the solids were washed with ethyl acetate (200 ml). The aqueous solution was made basic with concentrated ammonium hydroxide and extracted with ethyl acetate. The combined ethyl acetate solutions were washed with brine, then dried ($MgSO_4$) and removal of the solvent gave the crude base, which was chroma-tographed on silica gel (70 g). Elution with ethyl acetate, fractions 8-17 afforded, after removal of the solvent, 6.0 g (60%) of rac.-1-(4-benzyloxyphenyl)-2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone, b.p. 220-222 °C (0.005 Hgmm).

6.0 g of rac.-1-(4-benzyloxyphenyl)-2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone (0.014 mol) in acetone, on treatment with hydrogen chloride (anhydrous) afforded 6.0 g (92%) of rac.-1-(4-benzyloxyphenyl)-2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone•HCl, m.p. 197-198 °C.

EXAMPLE 19

rac.-erythro- and threo-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol

A mixture of 1.0 g (0.0025 mol) of rac.-1-(4-benzyloxyphenyl)-2-methyl-3-[4-(phenyl-methyl)-1-piperidinyl]-1-propanone•HCl in 100 ml of ethanol was hydrogenated over 0.4 g of palladium on carbon (10%) at room temperature and 50 psi for 17 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give 0.7 g of a mixture of diastereomeric salts rac.erythro-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol•HCl and rac.-threo-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol•HCl, which afforded, after crystallization from acetone-methanol, 0.5 g (61%) or pure rac.erythro-α-(4-hydroxy-phenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol hydrochloride as the hydrate, m.p. 185-186 °C.

A crude mixture of the diastereomeric salts, rac.-erythro-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidine-propanol •HCl and rac.-threo-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol•HCl, 0.5 g (0.0013 mol), obtained from a separate run was partitioned between methylene chloride and dilute ammonium hydroxide. The methylene chloride solution was washed with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure to give 0.3 g (67%) of a mixture

of diastereomeric alcohols, rac.-erythro-α-(4-hydroxyphenyl)-β-methyl-4-(phenyl-methyl)-1-piperidinepropanol and rac.-threo-α-(4-hydroxy-phenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol in a ratio of 5:1, which was chromatographed on silica gel (12 g). Elution with chloroform-methanol-water (90:15:10, v/v), fractions 6-14 afforded, after removal of the solvent and recrystallization of the residue from ether-hexane, 0.2 g (60%) of pure rac.-erythro-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol, m.p. 150-151 °C.

EXAMPLE 20

rac.-1-(4-Chlorophenyl)-2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone

A mixture of 6.7 g (0.04 mol) of 4-chloropropiophenone, 1.2 g of paraformaldehyde, 8.4 g (0.04 ml) of 4-benzylpiperidine hydrochloride in 40 ml dimethylformamide was stirred and heated in 55-60 °C for 20 hours. The reaction mixture was poured onto 1N hydrochloric acid and the precipitate was separated by filtration. The crude rac.-1-(4-chloro-phenyl)-2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone •HC1 was partitioned between ethyl acetate and dilute ammonium hydroxide. The ethyl acetate solution was washed with brine, then dried ($MgSO_4$) and removal of the solvent gave 5.0 g (35%) of rac.-1-(4-chlorophenyl)-2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone. For analysis a sample of this compound was distilled, b.p. 200-205 °C (0.06 Hgmm).

5.0 g (0.014 mol) of rac.-1-(4-chlorophenyl)-2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone on treatment with hydrogen chloride (anhydrous) in acetone gave 4.2 g (75%) of rac.-1-(4-chlorophenyl)-2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone•HC1, m.p. 199-200 °C. Analytical sample was recrystallized from acetone, m.p. 204-205 °C.

EXAMPLE 21

rac.-1-(2-Methyl-3-phenylpropyl)-4-(phenylmethyl)piperidine

A mixture of 2.0 g (0.005 mol) of rac.-1-(4-chlorophenyl)-2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone•HC1 in 150 ml of warm ethanol was hydrogenated (Parr Hydrogenator) over 0.8 g of palladium on carbon (10%) at room temperature and 50 psi fpr 17 hours. The catalyst was removed by filtration and the solvent concentrated to a low volume and to the mixture acetone was added. The crystals were separated by filtration, yield of rac.-1-(2-methyl-3-phenylpropyl)-4-(phenylmethyl)piperidine•HC1 is 1.0 g (56%), m.p. 177- 178 °C. For analysis a sample of this compound was recrystallized from ethanol-acetone, m.p. 177-178 °C.

An aliquot of the above salt rac.-1-(2-methyl-3-phenylpropyl)-4-(phenylmethyl)piperidine•HC1 was converted to the free base using ammonium hydroxide as base and ethyl acetate for extraction. For analysis, the base rac.-1-(2-methyl-3-phenylpropyl)-4-(phenylmethyl)piperidine was distilled, b.p. 168-170 °C (0.05 Hgmm).

EXAMPLE 22

Tablet Formulation (Wet Granulation)					
Item	Ingredients	mg/tablet			
		5mg	25mg	100mg	500mg
1.	(R*,S*)-rac-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	TOTAL	167	167	167	835
Manufacturing Procedure: 1. Mix Items 1, 2, 3 and 4 and granulate with purified water. 2. Dry the granulation at 50 °C. 3. Pass the granulation through suitable milling equipment. 4. Add Item 5 and mix for three minutes; compress on a suitable press.					

EXAMPLE 23

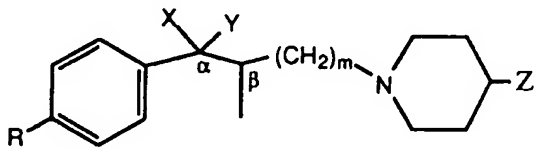
Capsule Formulation					
Item	Ingredients	mg/tablet			
		5mg	25mg	100mg	500mg
1.	(R*,S*)-rac-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	TOTAL	200	200	300	600
Manufacturing Procedure: 1. Mix Items 1, 2, and 3 in a suitable mixer for 30 minutes. 2. Add Items 4 and 5 and mix for 3 minutes. 3. Fill into a suitable capsule.					

EXAMPLE 24

Tablet Formulation (Wet Granulation)					
Item	Ingredients	mg/tablet			
		5mg	25mg	100mg	500mg
1.	[S-(R*,S*)] -α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol	5	25	100	500
2.	Lactose Anhydrous	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	2	2	5
	TOTAL	167	167	167	835
Manufacturing Procedure: 1. Mix Items 1, 2, 3 and 4 and granulate with purified water. 2. Dry the granulation at 50 • C. 3. Pass the granulation through suitable milling equipment. 4. Add Item 5 and mix for three minutes; compress on a suitable press.					

Claims

1. A compound of the formula



I

wherein
R is hydrogen, hydroxy, or aryl lower alkyloxy;
X is hydrogen;
Y is hydroxy or hydrogen;
or both X and Y taken together are oxygen;
Z is aryl lower alkyl; and
m is an integer from 1 to 4
or a diastereomer or an enantiomer thereof, except, the R,R diastereomer of formula I, wherein X is hydrogen, Y is hydroxy, R is benzyloxy, Z is benzyl, and m is 1,
or pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1, wherein m is 1 or 2.

3. A compound according to Claim 2, wherein R is hydrogen or hydroxy, Y is hydroxy and Z is benzyl or phenylethyl.

4. A compound according to Claim 3, wherein R is hydroxy, Z is benzyl and m is 1.

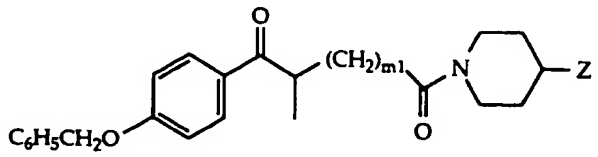
5. (R*,S*)-rac.-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol.

6. [R-(R*,S*)]-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol.

7. [S-(R*,S*)]-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol.

8. (R*,S*)-rac.-β-Methyl-α-[4-(phenylmethoxy)phenyl]-4-(phenyl- methyl)-1-piperidinepropanol;
(R*,S*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1 -piperidinepropanol;
rac.-4-[2-methyl-3-[4-(phenylmethyl)-1-piperidinyl]propyl]-phenol;
(R*,S*)-rac.-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinebutanol;
rac.-4-[2-methyl-4-[4-(phenylmethyl)-1-piperidinyl]butyl]-phenol;
(S)-2-methyl-1-[4-(phenylmethoxy)phenyl]-3-[4-(phenylmethyl)-1-piperidinyl]-1-propanone;
[R-(R*,S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol;
[S-(R*,S*)]-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol;
rac.-(2-methyl-3-phenylpropyl)-4-(phenylmethyl)piperidine and
(R*,R*)-rac-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol.

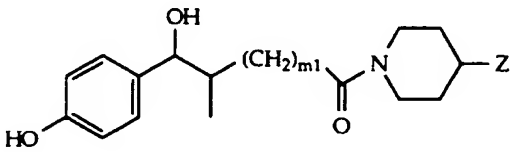
9. A compound of the formula



VII

wherein Z is aryl lower alkyl and m1 is an integer from 1 to 3.

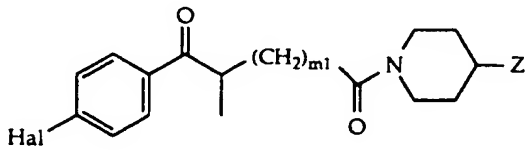
10. A compound of the formula



VIII

wherein m1 is an integer from 1 to 3 and Z is aryl lower alkyl.

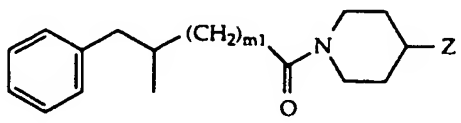
11. A compound of the formula



XII

wherein Hal is halogen, ml is an integer from 1 to 3, and Z is aryl lower alkyl.

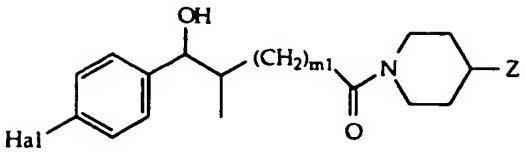
12. A compound of the formula



XIII

wherein m 1 is an integer from 1-3 and Z is aryl lower alkyl.

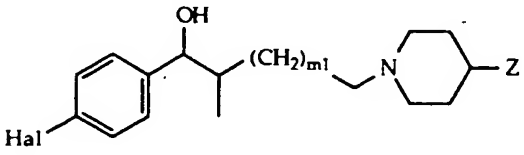
13. A compound of the formula



XIV

wherein Hal is halogen, m1 is an integer from 1 to 3 and Z is aryl lower alkyl.

14. A compound of the formula



XV

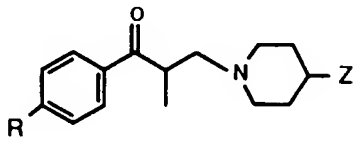
wherein Hal is halogen, m1 is an integer from 1 to 3 and Z is aryl lower alkyl.

15. Compounds in accordance with any one of Claims 1-8, for use as therapeutically active substances.

16. Compounds in accordance with any one of Claims 1-8 for use in the treatment of neurodegenerative diseases, such as ischemia, stroke and hypoxia.

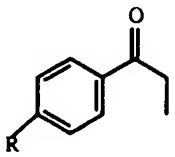
17. A process for the manufacture of a compound in accordance with any one of Claims 1-8, which comprises

a) for the manufacture of compounds of the formula



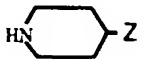
IA

wherein R and Z are as in Claim 1,
reacting a compound of the formula



II

wherein R is as in Claim 1,
with a compound of the formula



III

wherein Z is as in Claim 1,
and with paraformaldehyde, or

b) for the manufacture of compounds of the formula I, wherein X and Y are hydrogen, catalytically hydrogenating a compound of the formula I, wherein X and Y taken together and are oxygen, in the presence of a suitable catalyst such as palladium on carbon, or

c) for the manufacture of compounds of the formula I, wherein X is hydrogen and Y is hydroxy, reducing a compound of the formula I, wherein X and Y taken together and are oxygen, with hydrogen in the presence of a suitable catalyst such as palladium on carbon, or with a complex alkali metal hydride, such as lithium aluminium or potassium borohydride, or

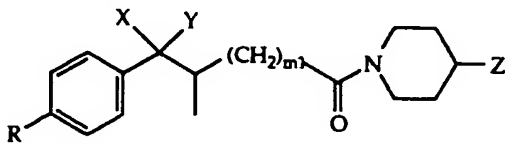
d) for the manufacture of compounds of the formula I, wherein X and Y are hydrogen, reducing a compound of the formula I, wherein X is hydrogen and Y is hydroxy with borane methylsulfide complex, or

e) for the manufacture of compounds of the formula I, wherein R is OH, debenzylating a compound of the formula I, wherein R is benzyloxy, or

f) for the manufacture of compounds of the formula I, wherein R is aryl lower alkoxy, reacting a compound of formula I, wherein R is hydroxy, with a corresponding aryl alkylhalide, or

g) for the manufacture of compounds of the formula I, wherein X and Y are taken together and are oxygen, oxidizing a compound of the formula I, wherein X and Y are hydrogen or X is hydrogen and Y is hydroxy, or

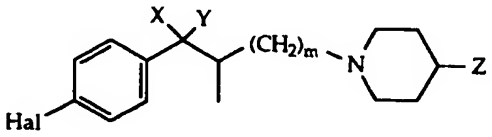
h) for the manufacture of compounds of the formula I, wherein X and Y are hydrogen or X is hydrogen and Y is hydroxy, reducing a compound of the formula



XVIII

wherein R, X, Y and Z are as in Claim 1 and m1 is 1-3,
with a complex alkali metal hydride or borane methylsulfide, or

i) for the manufacture of compounds of the formula I, wherein R is hydrogen, dehalogenating a compound of the formula



IXX

wherein X, Y, Z and m are as in claim 1 and Hal is halogen,
with hydrogen in the presence of a suitable catalyst such as palladium on carbon, or

j) for the manufacture of optically pure compounds of the formula I, resolving a racemic mixture into its enantiomeric components, or

k) for the manufacture of racemic compounds of the formula I, wherein X and Y are taken together and are oxygen, racemizing an corresponding optically pure compound, and

l) if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

18. A medicament containing a compound in accordance with any one of Claims 1-8 and a therapeutically inert excipient.

19. A medicament reducing adverse effects of neurotoxic injury to central neurons in accordance with Claim 18 for the control or prevention of neurodegenerative diseases, such as ischemia, stroke and hypoxia.

20. The use of a compound in accordance with any one of Claims 1-8 in the control or prevention of illnesses.

21. The use of a compound in accordance with any one of Claims 1-8 reducing adverse effects of neurotoxic injury to central neurons in the control or prevention of neurodegenerative diseases, such as ischemia, stroke and hypoxia.

22. The use of a compound in accordance with any one of Claims 1-8 for the manufacture of pharmaceutical compositions against neurodegenerative diseases, such as ischemia, stroke and hypoxia.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 11 2867

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	J.MED.CHEM., vol.34, 1991, WASHINGTON pages 3085 - 3090 CHENARD,B.L. ET AL. 'Separation of alpha-1 adrenergic and NMDA antagonist Activity in a Series of Ifenprodil Compounds' ---	1-22	C07D211/22 A61K31/445
Y	J.MED.CHEM., vol.34, 1991, WASHINGTON pages 90 - 97 ORNSTEIN,P.L. ET AL. '4-(Tetrazolylalkyl)piperidine-2-carboxylic acids. Poetent and selective....' ---	1-22	
Y	DRUGS, vol.44, no.3, 1992 pages 279 - 292 ROGAWSKI,M.A. 'The NMDA Receptor, NMDA Antagonists and Epilepsy Therapy' ---	1-22	
A	WO-A-92 08724 (AKTIEBOLAGET ASTRA) 29 May 1992 ---	1-22	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D A61K
A	WO-A-92 06957 (FISONS CORPORATION) 30 April 1992 ---	1-22	
A	WO-A-91 05787 (AMERICAN HOME PRODUCTS CORP) 2 May 1991 ---	1-22	
A	J.MED.CHEM., vol.33, 1990, WASHINGTON pages 2916 - 2924 HAYS,S.J. ET AL. 'New and versatile Approaches to the Synthesis of CPP-related competitive NMDA antagonists...' -----	1-22	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	30 December 1994	Stellmach, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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